

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 74-707

BIOEQUIVALENCE REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # 74-707

SPONSOR: Circa Pharmaceutical, Inc.

DRUG & DOSAGE FORM: Nicotine Polacrilex Gum, USP

STRENGTH: 4 mg

TYPE OF STUDY: SEE REVIEW

STUDY SUMMARY:

Acceptable (See Review)

PRIMARY REVIEWER: Chandra, S. Chaurasia, Ph.D.

INITIAL: CS

BRANCH: I

DATE: 2/24/99

TEAM LEADER: Yih Chain Huang, Ph.D.

INITIAL: YCH

BRANCH: I

DATE: 2/22/99

DIRECTOR, DIVISION OF BIOEQUIVALENCE: Dale P. Conner, Pharm.D.

INITIAL: DC

DATE: 2/23/99

DIRECTOR, OFFICE OF GENERIC DRUGS:

INITIAL: _____

DATE: _____

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANTS

ANDA:74-707


APPLICANT: Circa Pharmaceuticals, Inc.

DRUG PRODUCT: Nicotine Polacrilex gum, 4 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these regulatory reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,


Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Nicotine Polacrilex Gum, USP
4 mg/piece Chewing Gum
ANDA # 74-707
Reviewer: Chandra S. Chaurasia

Circa Pharmaceutical, Inc
Copiague, NY
Submission Date:
November 20, 1998

Review of an Amendment Requesting for a Biowaiver

I. Objective:

Review of Circa's amendment dated 11/20/98. The firm has submitted results of a chew-out study requested by the Agency.

II. Background

A summary background of the issues related to Circa's nicotine polacrilex gum 4 mg that is subject of this ANDA amendment is given below:

1. **Bio study.** On 07/06/95 and 03/28/96 Circa submitted an *in vivo* bioequivalence study (subjects=30) on its Nicotine Polacrilex Gum, 4 mg/piece, Lot #RD0965 (identified as the Original Product in the submission), comparing it to Marion Merrell Dow's Nicorette DS®, 4mg/piece, Lot #TF101A. The study (also identified as Bio Study 1 in this report) was found acceptable by the Agency (review date: 5/2/96, reviewer: Dr. Moo Park).
2. **Chew-out study.** Along with the above application, Circa also submitted an *in vivo* multiple dose crossover chew-out study (identified as Chew-out Study 1 in this report) in 8 subjects on its Nicotine Polacrilex Gum, 4 mg/piece, Lot #RD0965, comparing it to MMD's Nicorette DS®, 4mg/piece, Lot #TF101A. The release pattern (summarized in the table below) of nicotine was found comparable for the test and reference products

Table 1. Nicotine 4 mg Chew-out: Mean percentage nicotine release, n=8

Min.	Circa (TEST) Lot#RD0965	MMD (REF) Lot#TF101A
5	24.8	26.1
10	51.1	49.0
20	76.4	72.5
30	84.5	80.9

3. During an accelerated stability testing, Circa found problem with its **original** formulation (Lot #RD0965), and developed a **new** formulation (Lot #RD1203) manufactured in Oct. 1996. On August 14, 1997 the firm submitted an amendment requesting a waiver on its new formulation. The amendment was reviewed March 27, 1998 by Dr. M. Park. Background information related to this new formulation (Lot #RD1203) following its review by the Agency is briefly described below:

- 3.1. The amount of nicotine polacrilex resin in the new formulation was changed to _____ mg/piece compared to that of _____ mg in the original formulation to take into account of the _____ of nicotine in the resin when the amount of glycerin is decreased form to _____. It is also to be noted that there is a increase in sorbitol concentration in the new formulation over the original formulation (for a detail comparison of the compositions, please see Attachment I, Dr. Park's review: table 1, page 2).
- 3.2. Circa conducted a drug release test in water to compare the release profile of the new nicotine polacrilex glycerinated resin (_____ glycerin) and old nicotine polacrilex glycerinated resin (_____ glycerin) following USP method. Both old and new nicotine polacrilex resins showed fast nicotine release and met the USP specifications of NLT 70% in 10 minutes (For details please see Attachment I, table 2, page 3)
- 3.3. In the new formulation (i.e., Lot #RD1203), Circa used a different flavoring agent. Because of Agency's concern as to whether a better tasting nicotine gum might increase the potential for abuse of the new formulation, on Aug 14, 1997 the sponsor submitted a survey report conducted in adult smokers. The survey was conducted using a two-way cross over design comparing the new product with the RLD. The Agency reviewed the survey on April 15, 1998 (reviewer Dr. Moo Park), and found the taste and flavor of Circa's test product to be equivalent to those of reference product.
- 3.4. On April 2, 1998 the Agency issued a deficiency letter and recommended the firm to perform a chew-out study using the original formulation (Lot #RD0965) and new

formulations (Lot #RD1203) to evaluate nicotine release under use conditions.

The amendment of 11/20/98 is Circa's response to this deficiency.

In its response, the firm has reported its inability to conduct a chew-out study as suggested, primarily due to the fact that the batch of the Original Test (Lot #0965) formulation was made in 1994, and has expired.

Instead, the firm conducted a chew-out study comparing the new formulation (Lot #RD1203) against the reference listed drug Nicorette®DS.

III. Chew-Out Study Details:

Protocol No. 66-104: A Two-Way Crossover Multiple-Dose, Randomized Study to Characterize and Compare the Release Rate Profile of nicotine from Circa Polacrilex Gum, 4 mg and Nicorette Gum DS, 4 mg

A. Study Information

Clinical Site:

Principal Investigator:).

Clinical Dates: Beginning: 11/23/97; Ending: 11/23/97

Subjects: Entered - 14 normal healthy subjects (all males,
smokers 1-2 packets/day, 19-49 yrs old)
Completed - 14

Analytical Site: Circa Pharmaceuticals Inc., Copiague, NY

Analytical Dates: not provided, presumably completed 12/9/97
(please see Analytical Supervisor's sign-off,
Vol. 3.1, page 090)

Storage Period: not more than 20 days at -20 °C

Study Design: Multiple-dose, two-way crossover

Washout Period: 2-3 hours

Products tested:

Test Product: Nicotine Polacrilex Gum, 4 mg
Circa Pharmaceuticals, Inc., Lot #RD1203
Manufacturing Date 10/96; Expiration Date
(To Be Evaluated).

Reference Product: Nicorette® DS (nicotine polacrilex) gum, 4 mg
Marion Merrell Dow, Inc. Lot #YH 703A
Expiration Date 02/00

Randomization: A = reference , B = test

A,B: 1,4,5,8,10,11,14

B,A: 2,3,6,7,9,12,13

Inclusion/Exclusion Criteria:

Listed in Vol. 3.1 page 76. Subjects who participated in the study were all male smokers in the age range of 19-55 years.

Restrictions/Confinement:

Listed in Vol. 3.1, page 76. The subjects were not to take any alcoholic beverages 24 hours prior to or during each study period. The subjects were not to smoke 1 hour prior to the first dose of each study period and during each study period. Smoking was allowed following the last dose of Period 1, and during washout interval until 1 hour prior to the first dose of Period 2. Subjects were confined from 6:00 AM in the morning on the day of dosing, and until 12 hr after dosing.

Drug Administration:

Each subject in each period received four 4 mg oral doses (separated by at least an hour) of test or reference product as follows:

Dose Regimen	Time of Administration	Chewing Duration
First dose 1x4 mg gum	0 hr	30 minutes
Second dose 1x4 mg gum	1.5 hr	20 minutes
Third dose 1x4 mg gum	2.83 hr	10 minutes
Fourth dose 1x4 mg gum	4 hr	5 minutes

Subjects followed a controlled mastication pattern consisting of chews every seconds. The subjects chewed the gum times on of the mouth, and then moved the gum to the f the mouth. The rhythm of chewing was provided by an er.

Approximately one hour prior to the first dose, the subjects completed a 5 minute practice session using a placebo gum piece (vol. 3.1, page 079).

Gum Samples:

At the end of each chewing interval, the chewed gum from each subject was collected and stored in a separate, appropriately labeled glass container in a freezer at -20 °C. The samples from the first 12 subjects were sent to Circa for assay for remaining nicotine in the gum cud.

Study Results

Fourteen subjects completed the study.

Dropouts: none

Adverse events: No serious or unexpected adverse experiences occurred during the conduct of this study.

Nicotine Release Profile:

The mean nicotine releases obtained from the chew-out test at each time point were compared and the test/reference ratios were calculated as shown in Table 2. In each case the reference product released a higher percentage of nicotine (Table 2 and Figure 1-3). The mean differences in the percentage-label-claimed release rate range from 7.2% (for 5-minute time-point) to 11.6% (for 20-minute time-point). On the average, 9.5% greater *in vivo* release of nicotine was observed from the reference formulation as compared to that of the test formulation. This difference was found to be statistically significant.

While the Test/Reference ratios at 10-, 20- and 30-minute time-points were 0.79, 0.83, and 0.88, respectively, that for 5-minute time-point was 0.70.

Table 2. Percentage Nicotine Release in Chew-out Test
Arithmetic Means, n=12 (data as reported by the firm)*

Chewing time, min	Ref mean (\pm)	Test mean (\pm)	T/R ^a	Difference in % Release (Test vs. Ref)
5	24.2 (4.8)	17.04 (3.2)	0.70	-7.2%
10	44.09 (5.0)	34.82 (6.2)	0.79	-9.3
20	68.56 (7.3)	56.93 (8.4)	0.83	-11.6
30	79.73 (7.0)	70.28 (10.1)	0.88	-9.5

*Samples from the first 12 subjects only were sent to the analytical lab

^a Ratio of means of percentage-nicotine release in the test vs reference product

In its effort to draw a similarity vis-à-vis dissolution profile, the sponsor used f_2 test to compare the *in vivo* release profile of Test and Reference nicotine products. For details on this comparison please see Circa's report in Vol. 3.1, Appendix IV, page 131. The f_2 values for the new product (Lot #RD 1203) across the whole profile of 30 minutes were slightly greater than 50. For comparison it may be noted that these f_2 values for Circa's original product (Lot #0965) were greater than 75.

Due to the marginal f_2 values, though greater than 50 in chew-out Study 2 and statistically significant differences observed between test and reference formulations in nicotine release *in vivo* (as per sponsor's statement), Circa has provided a simulated bioequivalence report to determine whether these differences in chew-out Study 2 relate to differences in bioequivalence of the two products. Details of the methods used and results of bioequivalence simulations are presented in Appendix VI, Vol. 1.3, page 177). Briefly, the simulation was based on the following step by step approach:

- 1). The data from chew-out study 1 and 2 were used to determine the release rate constants of nicotine from the test and reference gum products.
- 2). The release rate constants from the chew-out study 1 were used to fit the nicotine plasma concentration observed in a previously conducted bioequivalence study (Biostudy 1) to obtain

the appropriate pharmacokinetic parameters, since both study used the same test formulation.

3). Plasma nicotine concentration data were simulated using the mean of the obtained pharmacokinetic parameters and the release rate constants from the chew-out study 2.

4). The bioavailability of the new test product formulation was compared to the Nicorette® DS 4 mg gum.

Results of this simulations study (as provided by the firm) is summarized below:

- The mean nicotine release rate constant (K_r) for the original Circa Nicotine Polacrilex 4 mg gum formulation (Lot #RD0965, chew-out Study 1, $K_r = 4.11 \text{ hr}^{-1}$) was not significantly different ($p = 0.3548$) from that of the Nicorette® DS 4 mg gum ($K_r = 3.85 \text{ hr}^{-1}$).
- The mean nicotine release rate constant for the new formulation (Lot #RD1203) of Circa Nicotine Polacrilex 4 mg gum ($K_r = 2.56 \text{ hr}^{-1}$) was significantly different ($p = 0.0001$) from that of the Nicorette® DS 4 mg gum ($K_r = 3.36 \text{ hr}^{-1}$, chew-out Study 2).
- Under the conditions of simulation, the new formulation of Circa nicotine polacrilex 4 mg gum meets the bioequivalence criteria when compared with the Nicorette® DS 4 mg gum. For example, the 90% confidence intervals for each of the parameters $\text{Ln}C_{\text{max}}$, LnAUC_{0-t} , and LnAUC_{0-i} for nicotine were within the acceptable bioequivalence limit of 80-125%.

Comments:

1. The mean *in vivo* nicotine release at all time points is 7-11% higher for the reference in comparison to that of the test drug, with an average 9.5% higher release for the reference than for the test product. The ratios of mean of percentage nicotine release in the test vs. reference product (T/R) for 20- and 30-minute time points are 0.83 and 0.88, respectively. The T/R ratios for 5-, and 10-minute time points are 0.73 and 0.79, respectively. However, the clinical significance of the nicotine release pattern at the first 5-10 minute during chew-out study is not known. Therefore, the chew-out study is acceptable.

It is to be noted that in an exactly similar situation with its new Nicotine Polacrilex gum 2 mg/piece formulation, the firm was asked to conduct a chew-out study to compare the original 2 mg formulation with the new 2 mg formulation. As in the present case, the original 2 mg formulation exhibited stability problem, and the new formulation has polacrilex matrix with glycerin compared to the in the original 2 mg formulation. Furthermore, due to the expiration of the original 2 mg Nicotine Polacrilex, the firm conducted a chew-out study comparing its new formulation of 2 mg strength with MMD's 2 mg, and found an average 6.4% higher release of nicotine from the test compared to that from the RLD at 10-, 20- and 30-minute time-points, where as that at the 5-minute time-point was almost the same in either case. The T/R ratios were in the range of 0.92 to 1.02 - well within the 0.8-1.25 range (for details see Attachment II, Dr. Park's review on 2 mg strength).

2. The in vitro release profile Circa's new nicotine polacrilex resin is similar to that of its old polacrilex formulation, and meets the USP specifications of NLT 70% in ten minutes.
3. The firm undertook a simulation bioequivalence trial and showed a bioequivalence between the test and reference product. It is to be noted that presently the Agency does not have a policy to grant bioequivalence based upon simulation studies.

V. Recommendations

The multiple-dose chew-out study Protocol No. 66-104, conducted by Circa Pharmaceuticals, on its Nicotine Polacrilex 4 mg, gum, Lot #RD1203, comparing it to Nicorette®, DS 4 mg, manufactured by Marion Merrell Dow, has been found acceptable by the Division of Bioequivalence.

The firm has satisfactorily responded to the deficiency issued by the Agency on April 2, 1998 and the application is now acceptable. The test product Nicotine Polacrilex 4 mg, gum is deemed bioequivalent to the reference listed drug Nicorette®, DS 4 mg gum manufactured by MMD.

/S/
Chandra S. Chaurasia
Review Branch I
Division of Bioequivalence

Date: 2/22/99

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FT INITIALED YHUANG

/S/ _____ Date: 2/22/99

Concur:

/S/ _____ Date: 2/23/99

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANTS

ANDA:74-707

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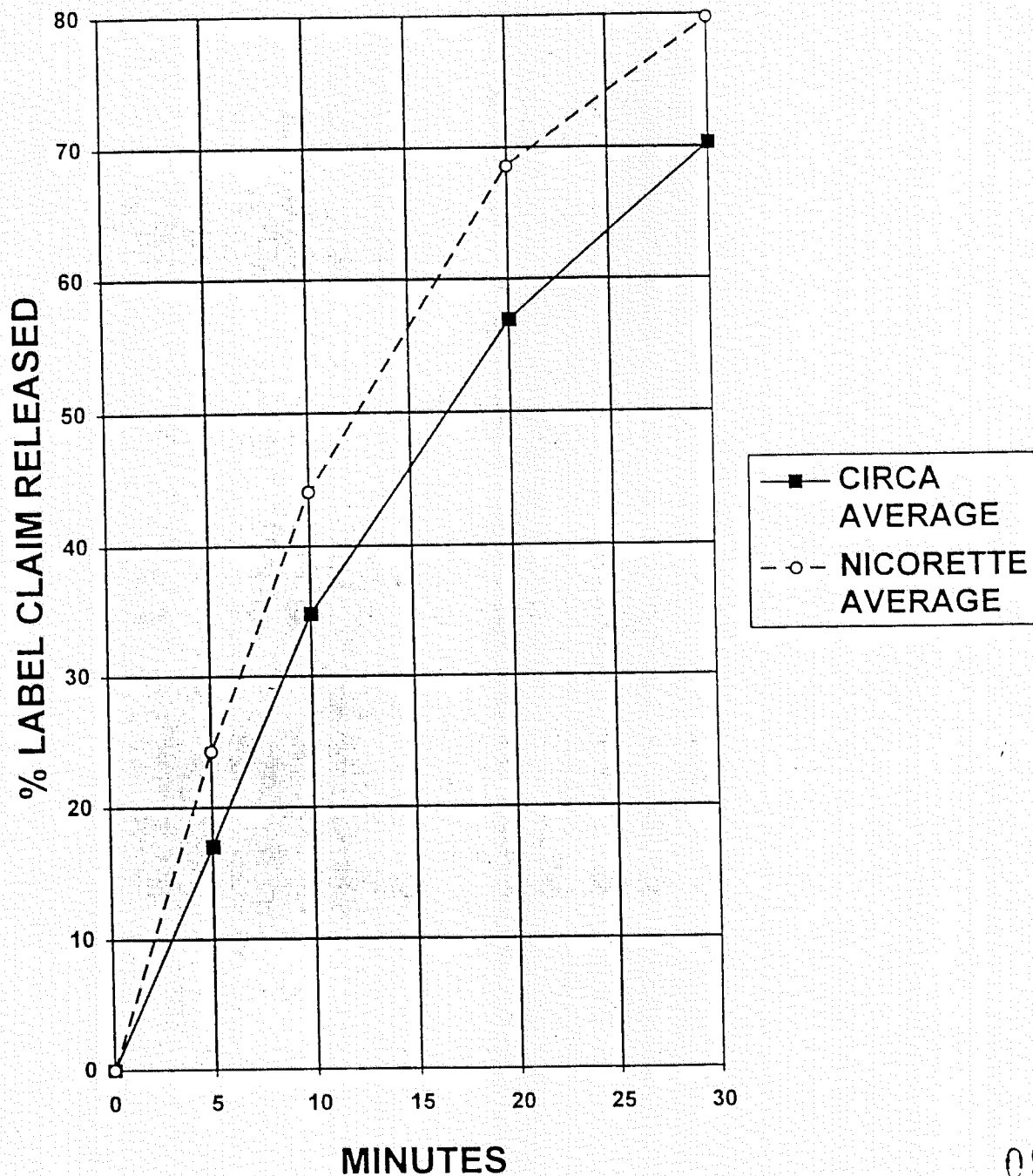

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Table 3. Composition of Old and New Formulations

Ingredient	Old Formulation mg/piece	New Formulation mg/piece
Nicotine Polacrilex Glycerinated glycerol) overage		g
Nicotine Polacrilex Glycerinated glycerol)+ overage	mg	
Sorbitol		
Sodium Carbonate		
Gum base		
Gum Flavor 3945		
Butylated Hydroxytoluene		
FD&C Green Color Blend		
Color Lake Blend		
Total gum weight	960.00	960.00

Fig. 1 (by sponsor)

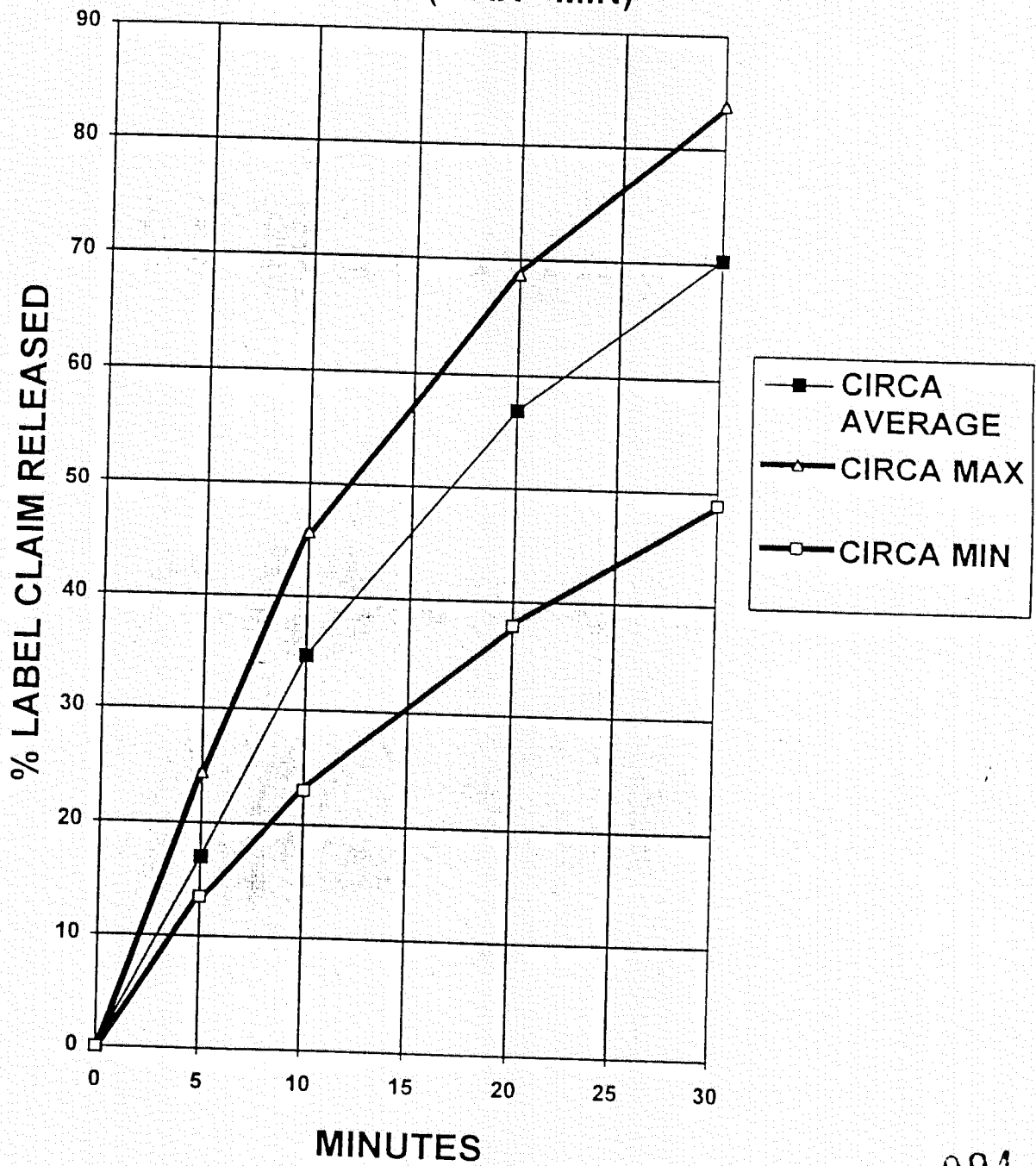
NICOTINE 4 MG GUM
PROTOCOL 66-104
AVERAGE OF ALL SUBJECTS
CIRCA vs. NICORETTE



093

Fig.2 (by sponsor)

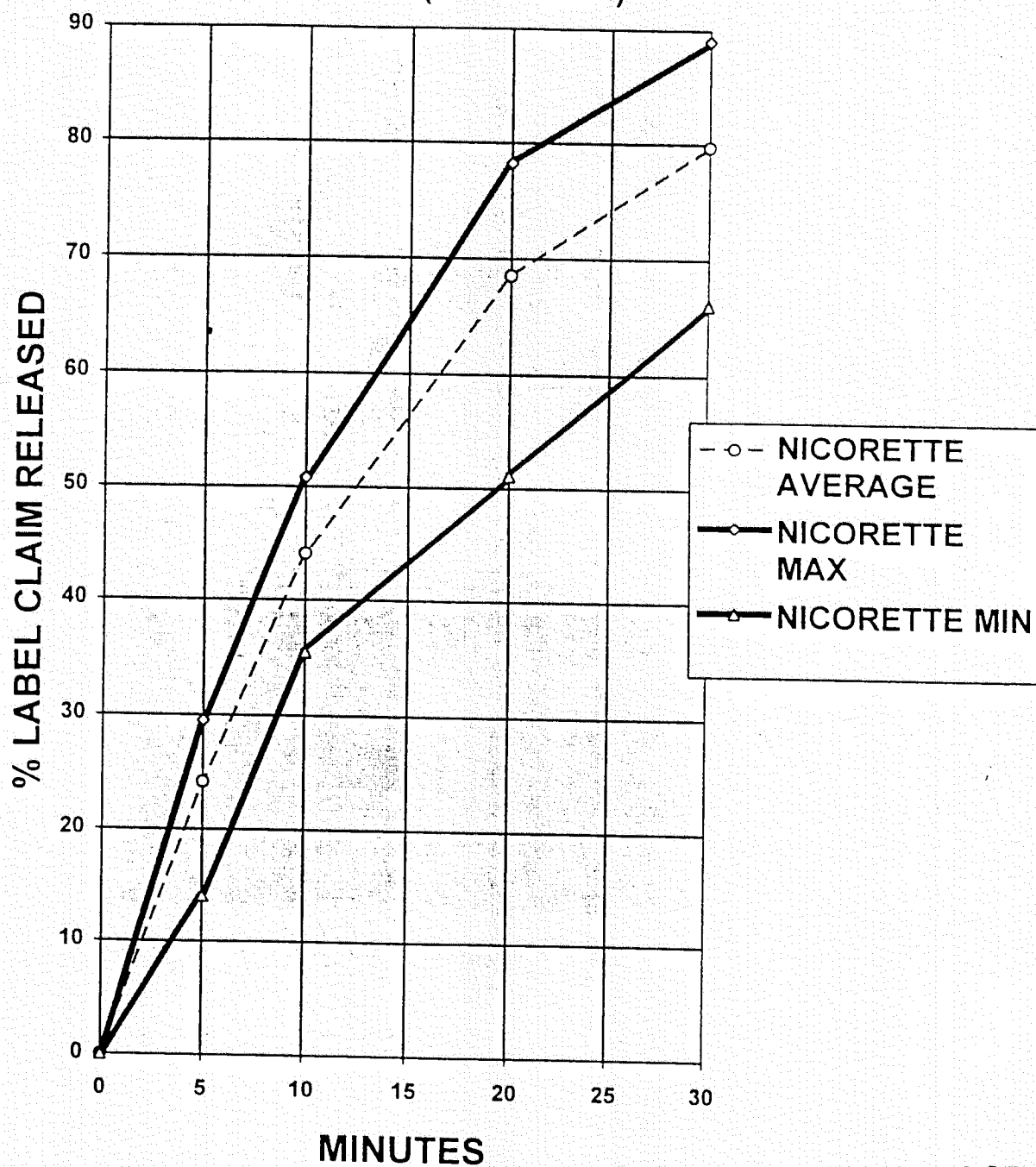
NICOTINE 4 MG GUM
PROTOCOL 66-104
CIRCA AVERAGE
(MAX - MIN)



094

Fig. 3 (by sponsor)

NICOTINE 4 MG GUM
PROTOCOL 66-104
NICORETTE AVERAGE
(MAX - MIN)



095